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MEETING REPORT

Banff 2019 Meeting Report: Molecular diagnostics in solid organ transplantation–Consensus for the Banff Human Organ Transplant (B-HOT) gene panel and open source multicenter validation

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This meeting report from the XV Banff conference describes the creation of a multiorgan transplant gene panel by the Banff Molecular Diagnostics Working Group (MDWG). This Banff Human Organ Transplant (B-HOT) panel is the culmination of previous work by the MDWG to identify a broadly useful gene panel based on whole transcriptome technology. A data-driven process distilled a gene list from peer-reviewed comprehensive microarray studies that discovered and validated their use in kidney, liver, heart, and lung transplant biopsies. These were supplemented by genes that define relevant cellular pathways and cell types plus 12 reference genes used for normalization. The

Abbreviations: ABMR, antibody-mediated rejection; B-HOT, Banff Human Organ Transplant; CLIA, Clinical Laboratory Improvement Amendments; DIP, data integration platform; DSA, donor specific antibody; FFPE, formalin fixed, paraffin embedded; MDWG, Molecular Diagnostics Working Group; TCMR, T cell–mediated rejection.

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770 gene B-HOT panel includes the most pertinent genes related to rejection, tolerance, viral infections, and innate and adaptive immune responses. This commercially available panel uses the NanoString platform, which can quantitate transcripts from formalin-fixed paraffin-embedded samples. The B-HOT panel will facilitate multicenter collaborative clinical research using archival samples and permit the development of an open source large database of standardized analyses, thereby expediting clinical validation studies. The MDWG believes that a pathogenesis and pathway based molecular approach will be valuable for investigators and promote therapeutic decision-making and clinical trials.

KEYWORDS

biomarker, biopsy, classification systems: Banff classification, clinical research/practice, diagnostic techniques and imaging, pathology/histopathology

1 | INTRODUCTION

The XV Banff Conference for Allograft Pathology was held on September 23-27, 2019, in Pittsburgh,Pennsylvania. One main topic, continuing a theme from two previous Banff meetings, was to include applications of molecular techniques for transplant biopsies and to articulate a roadmap for the clinical adoption of molecular transplant diagnostics for allograft biopsies.[1] This meeting report summarizes the progress made by the Banff Molecular Diagnostics Working Group (MDWG) and the resulting next steps from the 2019 conference.

2 | CHALLENGES IN MOLECULAR TRANSPLANT DIAGNOSTICS

The MDWG identified several challenges in the clinical application of molecular diagnostics. Different assays that measure different sets of genes validated for slightly different clinical contexts create a major analytical challenge. Enrolling patients into multicenter molecular diagnostic trials becomes problematic if local molecular diagnostic tests and risk stratification are done by noncomparable assays. The lack of a diagnostic gold standard for clinical validation of new molecular diagnostics requires multicenter standardization and independent validation in prospective randomized trials. Clinical and pathologic indications for molecular testing need to be defined and validated. Molecular tests must be cost effective to increase diagnostic utility beyond histopathology. For useful molecular diagnostics turnaround time needs to match immediate clinical needs. The integration of molecular tests with other diagnostic and clinical information requires standardization to make diagnosis and risk stratification comparable between centers. Industry partnerships are needed to advance the field, but transparency and appropriate disclosure of potential conflicts of interest are paramount. The MDWG believes that the present report shows a pathway that can address many of these issues.

3 | EVOLUTION OF MOLECULAR TRANSPLANT DIAGNOSTICS

Over the past 20 years, we estimate that more than 4000 organ transplant biopsies have been studied by whole transcriptome microarrays.[2] These have been conducted independently by several research groups, covering transplant biopsies of kidneys[3-7] and, to a lesser extent, other organs.[8-13] Different analytical approaches addressing relevant research questions from these data have been made available and reproduced by several research groups and transplant centers, covering a broad spectrum of phenotypes and patient demographics.[14] These studies led to potential diagnostic applications as well as major novel mechanistic insights with changes to the Banff classification, for example, the adoption of C4d-negative antibody-mediated rejection (ABMR) and chronic-active T cell–mediated rejection (TCMR) as new diagnostic categories.[3,14,15] Using transcriptome arrays the molecular phenotype in renal allografts correlates well with relevant rejection clinical entities and phenotypes.[2,16] In liver transplantation, microarray studies confirmed that liver biopsies with TCMR share very similar transcriptional phenotypes with those in renal allograft biopsies.[12,13] Transcriptional similarities are also present in heart and lung allograft biopsies.[8-11] These publications show that groups of genes within certain molecular pathways are statistically significantly associated with specific Banff histological lesions, rejection phenotypes, and Banff diagnostic categories. Transcript analysis also reveals potentially important underlying heterogeneities not perceived by pathology alone within diagnostic groups.[17]

In 2013 molecular diagnostics were added as an aspirational goal to the Banff classification.[15] The molecular quantification of endothelial cell associated transcripts and classifier-based prediction of donor specific antibody-mediated tissue injury were adopted as diagnostic features/lesions equivalent to C4d for the diagnosis of ABMR. This was noted to be a forward-looking proposal at the time, because there was no consensus around which endothelial genes should be quantified and no independent multi-institutional validation for any diagnostic classifier or gene set. The main impetus in 2013 to adopt a molecular diagnostic option into the classification,

despite these limitations, was to set the future direction for the Banff classification and to promote collaborative and multi-institutional, open source efforts to advance the field by validating, standardizing, and making molecular transplant diagnostics accessible to the broad transplant community. This is a foundational value of the Banff consortium.[18]

At the 2015 meeting, the Banff MDWG recommended the creation of molecular consensus gene sets as classifiers derived from the overlap between published and reproduced gene lists that associate with the main clinical phenotypes of TCMR and ABMR.[1] Similar roadmaps and processes for clinical adoption have been reviewed extensively and proposed by other key opinion leaders in the field.[19-22] Collaborative multicenter studies were proposed to close identified knowledge gaps and enable practical molecular diagnostic incorporation into diagnostic classifications.[22] The 2017 Banff meeting identified an initial validated, consensus gene list with potential specific indications for molecular testing.[23] Importantly presented at this meeting was a new technology, Nanostring, which uses robust multiplex transcript quantitation from formalin-fixed, paraffin-embedded (FFPE) biopsies. The compelling advantage of NanoString is that it performs transcriptional analysis on routine histological samples allowing correlation of both histologic with molecular phenotypes on the same tissue.[1]

4 | CURRENT STATE OF MOLECULAR TRANSPLANT DIAGNOSTICS

Most of the published research studies for molecular testing on biopsies has been performed using microarrays on an extra biopsy core stored in RNAlater Stabilization Solution. The pioneering work by Halloran and colleagues was the basis of a commercial test (Molecular Microscope MMDx) now offered by One Lambda Inc.[17,24-26] These insightful, prospective studies showed strong associations of transcript patterns with the histological Banff lesions and diagnosis but also identified discrepancies.[17] These discrepancies require further investigation to reveal the optimal integration of histology and molecular biopsy features that are informative of outcome and response to therapy. No prospective randomized outcome trial using microarray assays as the end point has been conducted, in part because of the technical challenges and the long follow-up required. Although microarray analysis is the most established method for biopsies, alternative approaches, less invasive than a biopsy, are attractive and under investigation, such as urine and blood transcript analysis.

Recently, more practical technologies based on FFPE biopsy analysis are now available, in particular the NanoString nCounter system (NanoString Technologies, Seattle, WA). Several NanoString publications using FFPE transplant specimens identify similar transcript associations with the molecular and histologic phenotypes as those reported in microarray studies.[3,4,13-18,27-29,29-33] Among the advantages of NanoString are (1) a separate core processed at the time of biopsy is not required; (2) transcripts are assessed in the same sample analyzed by light microscopy; and (3) large retrospective and longitudinal analyses of archived samples can be readily performed in the setting of multicenter studies, which will enable retrospective randomization with long-term survival end points available (Table 1).[27] Over 1000 publications have reported its application and value. The NanoString system yields comparable results between FFPE and fresh frozen samples, with a higher sensitivity than that of microarrays and about equal to reverse transcription polymerase chain reaction (RT-PCR).[34-36] This technology in one assay uses color-coded molecular barcodes that can hybridize directly up to 800 different targets with highly reproducibility. NanoString thereby closes a gap between genome-wide expression (ie, microarrays and RNA sequencing as whole transcriptome discovery platforms) and mRNA expression profiling of a single target (ie, RT-PCR). But unlike quantitative RT-PCR, the NanoString system does not require enzymes and uses a single reaction per sample regardless of the level of multiplexing. Thus, it is simpler for the user and requires less sample per experiment for multiplex experiments, for example, pathway analysis, assessment of biomarker panels, or assessment of custom-made gene sets. The NanoString system is approved for clinical diagnostics and paired with user-friendly analytical software, thus representing a simple, relatively fast (24-hour turnaround time), automated platform that is well poised for integration into the routine diagnostic workflows in existing pathology laboratories.[37] Synthetic DNA standard oligonucleotides, corresponding to each target probe in the panel, allow normalization of expression results between different reagent batches, platforms, and users, This permits standardization of diagnostic thresholds across multiple laboratories, a major challenge using microarrays and RNA sequencing.[27] A major disadvantage of the NanoString approach is the need to predefine the gene panel and the restriction to 800 probes, making it better for follow-up studies once the discovery phase with microarrays has winnowed the possibilities to the most informative transcripts. The other disadvantages, shared with microarrays and RNASeq, is the loss of anatomic localization and the need for a biopsy.

5 | GENERATION OF A BANFF HUMAN ORGAN TRANSPLANT (B-HOT) PANEL

The B-HOT panel includes the validated genes found informative from major peer reviewed microarray and NanoString studies on kidney, heart, lung, and liver allograft biopsies, identified by the MDWG through literature review. A list of the genes with corresponding key publications is given in the Data S1. In detail, candidate genes were identified using the key words “transplantation,” “kidney, “heart, ” “lung, ” ‘liver, ” “gene expression, ” “molecule, ” and “transcripts. ” Mining these publications for genes listed as significantly associated with any study variable revealed 2521 publications indexed in PubMed concerning more than 4000 genes. After redundant and duplicate genes were removed, the list contained 1749 genes. Then the MDWG members identified overlap between these genes and genes described in the peer-reviewed

TABLE 1 Technical comparison of gene expression analysis using formalin-fixed paraffin-embedded (FFPE) tissue with NanoString nCounter vs fresh tissue with DNA microarrays

Feature	FFPE tissue with NanoString nCounter	Fresh tissue with cDNA microarrays
Maximum number of transcript targets	800	>47 000[a]
Off-the-shelf panels available	Yes	Yes
Custom panels available	Yes	Yes
Recommended RNA input quantity	100 ng	50-500 ng
Requires reverse transcription/ amplification	No	Yes
Approximate assay turnaround time[b]	24-40 h	25.5-37.5 h
Analysis software provided by manufacturer	Yes[c]	Yes[d]
Ability to use same sample for histology and gene expression analysis, that is, ability for histomolecular integration	Yes	No
Immediate access to long-term clinical follow-up data on archival clinical samples (FFPE)	Yes	No
Food and Drug Administration approved	Yes for platform Yes for specific clinical assays[e]	No for platform Yes for specific clinical assay[f]
Approximate assay cost per sample[g]	$275	$1000-3000
Integration with local (decentralized) clinical workflow	Simple due to local testing (no shipment of samples) on regulatory approved platform using simple open source analytics	Complex (shipment of sample to referral lab, no regulatory approval of platform, complex analytics)

[a]Affymetrix GeneChip Human Genome U133 Plus 2.0 Array.

[b]Dependent on multiple variables: instrument settings, RNA input quantity, technician experience, etc. Time excludes RNA extraction time and sample shipment time if applicable.

[c]NanoString nSolver Analysis Software.

[d]Affymetrix Transcriptome Analysis Console Software.

[e]NanoString Prosigna Breast Cancer Prognostic Gene Signature Assay.

[f]Roche AmpliChip CYP450 Test, a pharmacogenetics assay to determine the genotype of two cytochrome P450 enzymes: 2D6 and 2C19.

[g]Including RNA isolation but excluding instrument expenses and labor for RNA extraction. Reagent cost varies with number of transcript targets and samples. Microarrays costs vary on scale of economy by provider.

literature[2,8,12,29,32,33,38-50,9,51,52,10,53-56,11,57-64,65] as being strongly associated with relevant clinical phenotypes and identified 1050 genes to be considered for inclusion. In the next step, a list including all genes with consensus expert opinion were selected and for which all Hugo duplicates were then combined, leaving 670 unique genes.

We initiated discussions with NanoString and learned they would be willing to make our panel widely available. However, their commercial panels typically have 770 genes, so they provided suggestions for addition genes to delineate relevant cellular pathways and cell types that have been used in other panels. Using an independent data-driven process, NanoString Technologies Inc recommended additional genes within relevant molecular pathways related to the 670 genes that were most informative by their Ingenuity Pathways. The final B-HOT panel included 758 genes covering the most pertinent genes from the core pathways and processes related to host responses to rejection of transplanted tissue, tolerance, drug-induced toxicity, transplantation-associated viral infections (BK polyomavirus, cytomegalovirus, Epstein-Barr virus) plus 12 internal reference genes for quality control and normalization (Figures 1 and 2, Table 2). Through that approach the B-HOT gene panel was defined, further engineered, and made commercially available (https://www.NanoString.com/products/gene-expression-panels/gene-expression-panels-overview/human-organ-transplant-panel). The pathways

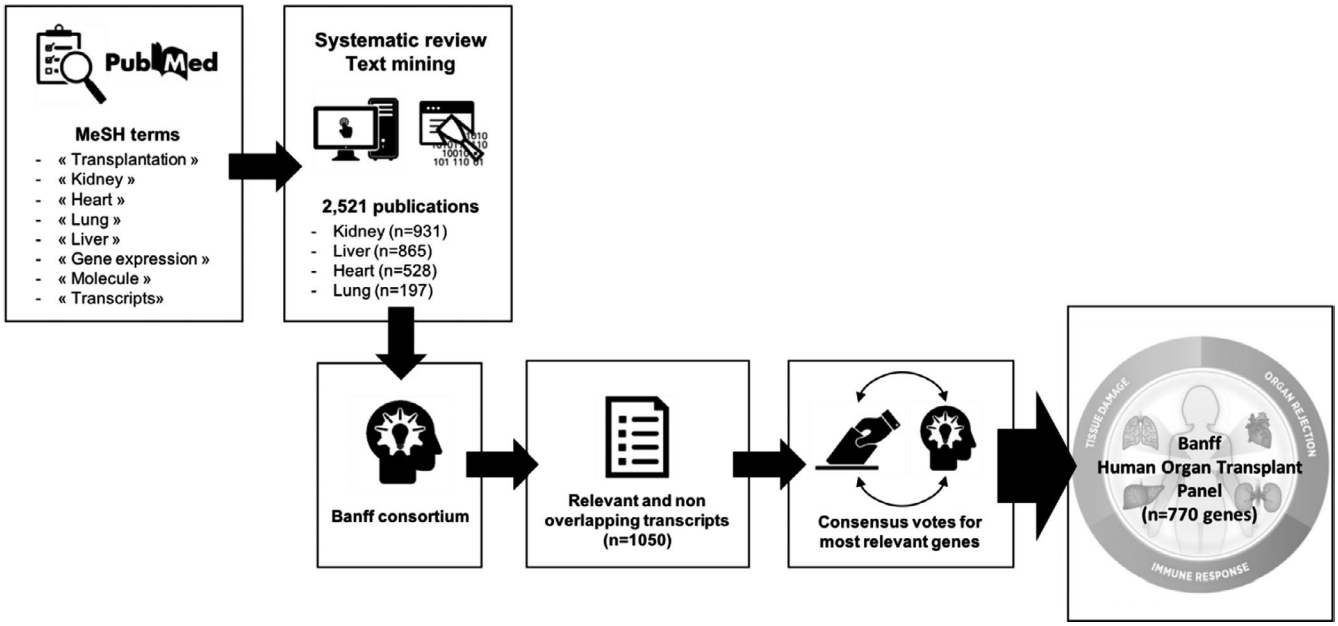

FIGURE 1 Banff Human Organ Transplant (B-HOT) panel design process and main pathways investigated by this panel. Banff Human Organ Transplant (B-HOT) panel design process involved 12 transplant expertsfrom 5 universities (Harvard University, Université de Paris, University of Alberta, Imperial College of London, and Erasmus MC Rotterdam). Banff consortium was composed of B. Colvin, R.N. Smith, I. Rosales, M. Mengel, B. Adam, C. Roufosse, M.C. Clahsen-van Groningen, J.H. von der Thüsen, B. Robin, J. Dagobert, J.-P. Duong-van-Huyen, and A. Loupy. The Banff Human Organ Transplant Panel logo in Figure 1 has been reproduced with permission from NanoString

added to the list are given in Figure 2 and in more detail in the Table S1.

The panel probes were also designed to cover different organ types for transplantation and for sequence homology with non-human primates to facilitate preclinical research applications. The panel's broad coverage of inflammatory, adaptive, and innate immune systems; signaling; and endothelial transcripts will likely be largely applicable across organ types but with some expected organ specific variation. Furthermore, parenchymal transcripts will often be organ specific and many have been included (see Table S1). We anticipate that continued discovery of other informative transcripts not included in the B-HOT panel will occur. To provide flexibility, up to 30 custom genes can be added to the B-HOT panel by an investigator. Although the panel has been commercialized for the nCounter platform, the gene list is not proprietary and probes based on the gene list can be designed to run on any transcript analytical platform.

6 | NEXT STEPS: MULTICENTER ANALYTICAL AND CLINICAL VALIDATION

The Banff MDWG formed a voluntary, growing, and open international consortium, independent of commercial sponsorship, to develop future steps for validation, analyses, and database sharing. The focus of the next 2 years will be validation of the panel and discovery of the optimal algorithms and gene sets. This will be enabled by (1) the B-HOT panel and its comprehensive probe standards for comparison between laboratories, batches, and runs; (2) a shared database containing clinical, laboratory, pathological and transcript data; and (3) access to comprehensive sophisticated bioinformatics. The next steps will be to document the analytical validity across laboratories and then determine the clinical validity. The clinical validity will be assessed by analyzing B-HOT transcripts in 1000 or more clinical biopsies (as of this report the consortium has run the B-HOT panel on over 600 samples). These results along with standardized clinical and pathologic information will be entered in a shared database, which will be interrogated to discover the most useful algorithms for clinical applications.

Analytical validation for regulatory approval must document accuracy, precision, analytical sensitivity (reproducibility, coefficient of variance), reportable ranges, reference interval values, and analytical specificity. Calibration and control procedures must be determined, and the laboratory must be enrolled in external proficiency testing programs. Clinical validation is the next step. Even an assay with perfect analytical validity does not automatically imply association between the test result and a relevant clinical outcome or action. This requires access to relevant patient populations' material of adequately powered sample size to evaluate assay performance in a real-world clinical setting. Accordingly, clinical utility of an assay needs to be established by providing evidence of improved, measurable clinical outcome or benefit that is directly related to the use of the test, that is, proof that the test adds significant value to patient care. This also needs to take into consideration how the assay is interpreted, reported, and applied in the context of clinical patient management. Ideally, proper evaluation of an assay's clinical utility requires prospective randomized control trials.[66]

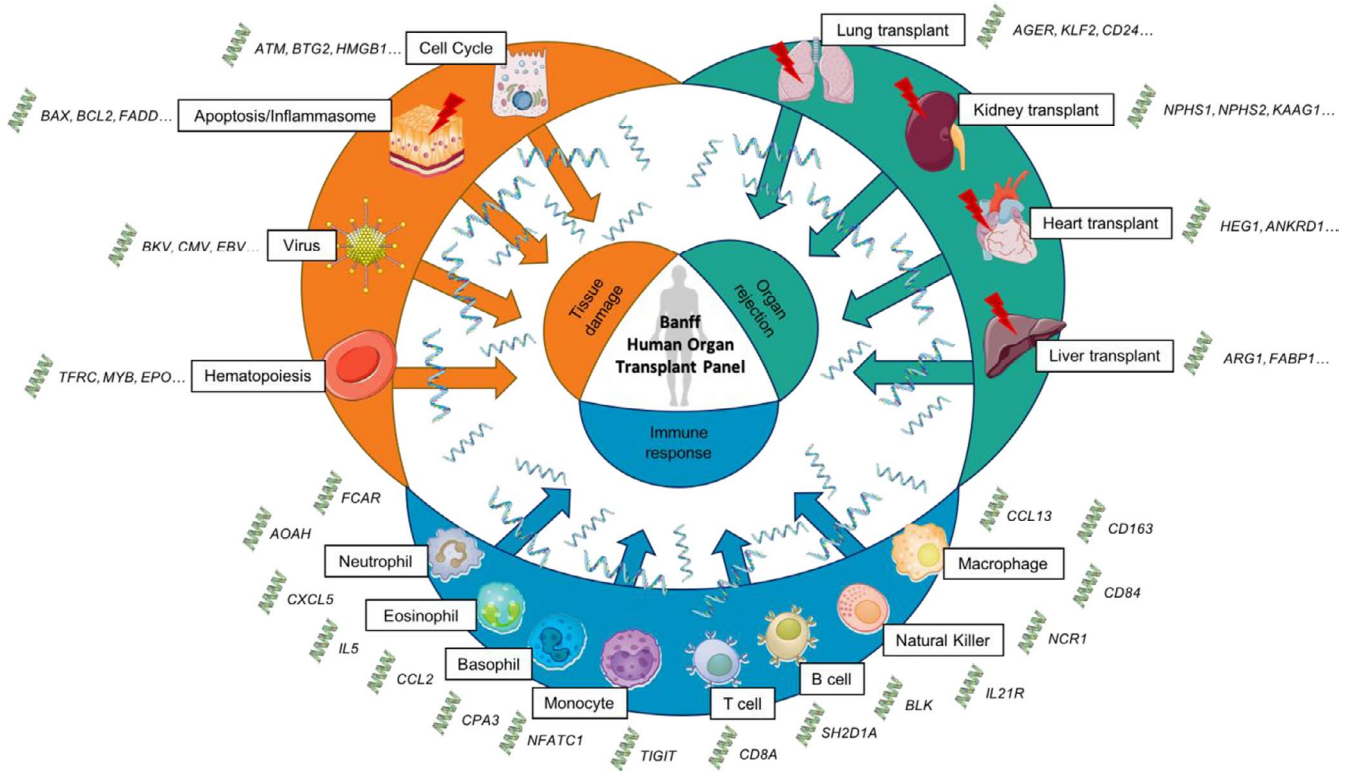

FIGURE 2 Examples of cells, pathways, and genes studied by the B-HOT panel. Three main pathways can be identified: tissue damage, organ rejection, and immune response. The B-HOT panel profiles a total of 758 genes across 37 pathways. Green double-stranded DNA represents gene expression, blue single-stranded RNA represents RNA expressed by cells or tissue. Cartoons of organs, cells, and other illustrations used in Figure 2 have been retrieved from http://smart.servier.com/, a free medical images bank of Servier

The B-HOT panel will undergo all of these validation steps. In the next 2 years retrospective, well-annotated cohorts will be analyzed for analytical and clinical validation. The MDWG is aligning joint efforts using available NanoString systems at participating centers for studying a broad spectrum of archived and well-annotated transplant biopsies. To centralize the resulting multicenter molecular data from archived transplant biopsies together with the related clinical and outcome data, algorithms, and tools for analysis (including explorative analytics, machine learning-based diagnostic approaches/classifiers, and risk prediction tools) with remote access by users across the world, a data integration platform (DIP) will be built[67] (Figure 3). Participating centers will be able to upload routinely collected transplant-related patient data in an anonymized and uniform fashion. A participating investigator will then be able to use all data in the DIP. Currently underway is the development of a consensus data template representing the variables and units to be included in the DIP. The NanoString data files also include important analytical parameters (quality control measures, background subtractions, normalization values) in addition to the individual gene expression values, which will also be part of the DIP to allow for standardization across laboratories and thus multicenter analytical validation of any diagnostic assays. The output of this effort is expected to be a robust well-characterized gene set (presumably a subset of the B-HOT panel or additional genes) and analytic methodology for interpretation, which will be presented at a subsequent Banff meeting and published. We expect to see correlations with histologic diagnosis (including interpretations not revealed by routine pathology analysis), ongoing immunosuppressive therapy, prediction of outcome, and response to treatment. We (and others, we hope) will follow this by prospective, controlled clinical trials to fully define clinical utility.

As a first evaluation, after the Banff meeting, a member of the MDWG, Neal Smith, performed an in silico assessment of the B-HOT panel genes using the archived Genomic Spatial Event databases from Halloran's group[5,46,68] that contains 764 kidney biopsy samples with microarray data and diagnostic classification as TCMR, chronic-active ABMR, mixed, acute kidney injury, no rejection, and normal. Briefly, 3 bioinformatics methods were used to see if they could identify the 6 diagnostic groups from the transcripts: (1) supervised, using diagnostic and pathogenesis based transcripts sets of Halloran;[16] (2) semisupervised, using Nanostring pathways (Data S1) plus CIBERSORT cells types; and (3) unsupervised principal component analysis. Results confirmed the correlation of expected gene sets in each analysis with the 6 diagnostic categories (Smith, manuscript in preparation). A description of the initial B-HOT results in kidney transplants to be presented at the 2020 American Transplant Conference reveals both expected and novel correlations with pathologic categories.[69]

The B-HOT panel will be commercially available for research use only. Whether B-HOT leads to a clinically indicated laboratory

TABLE 2 List of the 770 genes integrated in the HOT panel and their related pathways. Four groups (Tissue and cellular process, Immune system, Organ specific, Viral infection) and 17 subgroups define the genes. Twelve genes are used for internal reference. Genes can possibly be related to other pathway or involved in several processes

Tissue and cellular process					**Immune system**				
Angiogenesis	CDH13	JAK1	PTGER4	TIMP1	**Adaptive Immune System**	**Chemokine Signaling**	CD209	HFE	NFKB1
ADAMTS1	CDH5	JAK2	PTGS2	TIPARP	AIRE	ACKR1	CD83	ICAM1	NLRC5
ADGRL4	CDKN1A	KDR	PTPN2	TM4SF1	BLNK	CCL4	CSF1	ICAM2	NOD2
ENG	CGAS	KIT	PTPN22	TM4SF18	BST2	CCL5	CSF3R	IFI44	NOS2
ERG	CHCHD10	KITLG	PTPN6	TMEM178A	BTK	CCR2	FCER1A	IFNG	OASL
MMRN2	CITED4	KLF2	PTPRO	TNC	CCR7	CCR4	FCGR2A	IFNGR1	OSMR
VEGFA	CLEC4C	KLF4	RAB40C	TNFAIP6	CD19	CCR5	FCGR3A/B	IFNGR2	PAX5
VEGFC	COL13A1	KLHL13	RAF1	TNFRSF1A	CD22	CMKLR1	GNLY	IKBKB	PDCD1
VWF	COL1A1	LAMP1	RAMP3	TP53	CD247	CX3CL1	GZMH	IKBKG	PDPN
Apoptosis	COL3A1	LAYN	RAPGEF5	TPMT	CD274	CX3CR1	GZMK	IKZF1	PECAM1
BAX	COL4A1	LCN2	RARRES1	TPSAB1/B2	CD276	CXCL1/2	IFI27	IL10	PIK3CD
BCL2	COL4A3	LEF1	RASIP1	TRAF6	CD28	CXCL10	IFNA1	IL10RB	PIK3CG
BCL2A1	COL4A4	LHX6	RASSF9	TRIM22	CD3D	CXCL11	IL1B	IL12A	POU2AF1
BCL2L1	COL4A5	LIF	RELA	VCAN	CD3E	CXCL12	IL33	IL12B	PPBP
BCL2L11	CRIP2	LOX	RGN	VMP1	CD3G	CXCL13	KLRB1	IL12RB2	PRF1
BIRC3	CSF2RB	LRP2	RHOJ	WARS	CD4	CXCL2	KLRC1	IL13	PTPN7
CASP1	CTNNB1	LRRC32	RHOU	WNT9A	CD40LG	CXCL5	KLRD1	IL15	PTPRC
CASP3	CTSL	LTBR	RNF149	ZEB1	CD45R0	CXCL8	KLRG1	IL16	PVR
CASP4	DCAF12	LYVE1	ROBO4	**Hematopoiesis**	CD45RA	CXCL9	KLRK1	IL17F	SELL
CASP8	DDX50	MAF	RORA	CD34	CD45RB	CXCR3	NKG7	IL17RC	SELPLG
CFLAR	DNMT1	MALL	RORC	CSF2	CD7	CXCR4	NOD1	IL1A	SERINC5
FADD	DNMT3A	MAP3K1	RPL19	EPO	CD72	CXCR6	PSTPIP1	IL1R1	SIGIRR
FAS	DUSP2	MAPK11	RPS6	FLT3	CD79A	PF4	SAMHD1	IL1R2	SIGLEC5
FASLG	ECSCR	MAPK12	RPS6KB1	GATA3	CD86	**Complement System**	TAPBP	IL1RAP	SLAMF6
GIMAP5	EDA	MAPK13	RTN4	IKZF2	CD8A	C1QA	TLR2	IL1RN	SLAMF7
IFI6	EEF1A1	MAPK14	RXRA	IL12RB1	CD8B	C1QB	TLR3	IL21	SLAMF8
NLRP3	EGFR	MAPK3	S100A12	IL5	CTLA4	C1S	TLR4	IL21R	SLPI
RGS5	EGR1	MAPK8	S100A8	IL6	CXCR5	C3	TLR5	IL23A	SMAD5
TNFRSF1B	EHD3	MARCH8	S100A9	IL7	FAM30A	C3AR1	TLR7	IL23R	SOCS1
TNFRSF4	EMP3	MCM6	S100B	LCK	FCAR	C5	TLR8	IL27	SOCS3
TNFSF10	EPAS1	MEF2C	S1PR1	MYB	GZMB	C5AR1	TLR9	IL27RA	STAT4

(Continues)

TABLE 2 (Continued)

Tissue and cellular process					Immune system				
XAF1	ERRFI1	MEGF11	SCGB1A1	RUNX1	HLA-A	C9	TREM1	IL2RA	STAT6
CellProcess	EVA1C	MEOX1	SDC1	TFRC	HLA-B	CD46	**Other Immune Genes**	IL2RG	TBX21
ABCB1	EZH2	MERTK	SELP	**Metabolism**	HLA-C	CD55	ACVRL1	IL4R	TCF7
ABCC2	F3	MET	SEMA7A	ABCA1	HLA-DMA	CD59	ADAMDEC1	IL6R	TCL1A
ABCE1	FGD2	MIR155HG	SERPINA3	ALDH3A2	HLA-DMB	CFB	AGER	IL6ST	TIGIT
ACVR1	FKBP1A	MMP12	SERPINE1	ALOX15	HLA-DPA1	CFH	BCL6	IL7R	TNFRSF14
ADAM8	FN1	MMP14	SERTAD1	APOE	HLA-DPB1	CFI	BTLA	INPP5D	TNFRSF9
ADORA2A	FOS	MMP9	SHROOM3	APOL1	HLA-DQA1	CR1	CALHM6	IRF1	TNFSF14
AGR2	FOSL1	MT1A	SIRPG	APOL2	HLA-DQB1	MASP1	CCL2	IRF4	TNFSF18
AGR3	FOXO1	MT2A	SKI	ARG2	HLA-DRA	MASP2	CCL21	IRF6	TNFSF9
AGT	FOXP3	MTOR	SLA	B3GAT1	HLA-DRB1	MBP	CCR3	IRF8	TOX2
AHR	FPR1	MUC1	SLC11A1	CAV1	HLA-DRB3	SERPING1	CD160	ITGAM	TRIB1
AICDA	FYN	MX2	SLC19A3	CETP	HLA-E	**Inflammatory Response**	CD163	ITGAX	TYK2
AIM2	GBP1	MYBL1	SLC22A2	CH25H	HLA-F	ALOX5	CD1D	JAK3	VCAM1
AKR1C3	GBP2	MYC	SLC25A15	CRHBP	HLA-G	ANXA1	CD2	KIR_Activating_Subgroup_1	VSIR
ALAS1	GBP4	NFIL3	SLC4A1	GAPDH	ICOS	AOAH	CD24	KIR_Activating_Subgroup_2	XCL1/2
ANKRD1	GDF15	NOS3	SMAD2	HSD11B1	ICOSLG	CARD16	CD244	KIR_Inhibiting_Subgroup_1	
ANKRD22	GEMIN7	NOTCH1	SMAD3	IDO1	IFI30	CARD8	CD27	KIR_Inhibiting_Subgroup_2	
APOLD1	GNG11	NOTCH2	SMAD4	IGF1	IGHA1	CCL13	CD40	KIR3DL1	**VIRAL INFECTION**
AQP1	HAVCR1	NOX4	SMARCA4	LDLR	IGHG1	CCL15	CD48	KIR3DL2	
AREG	HDAC3	NPDC1	SOD2	NNMT	IGHG2	CCL18	CD5	KLRF1	**Virus**
ARG1	HDAC6	NPPA	SOST	PLA1A	IGHG3	CCL19	CD58	LAG3	BK large T Ag
ARHGDIB	HDC	NPPB	SOX7		IGHG4	CCL20	CD6	LAIR1	BK VP1
ARRB2	HEG1	NR4A1	SP100		IGHM	CCL22	CD68	LAP3	CMV UL83
ASB15	HIF1A	OR2I1P	SP140	**ORGAN SPECIFIC**	IGKC	CCL3/L1	CD69	LGALS3	EBV LMP2

(Continues)

TABLE 2 (Continued)

Tissue and cellular process					Immune system				
ATF3	HK2	P2RX4	SPIB		IGLC1	CCR10	CD70	LILRB1	**Viral Detection Genes**
ATM	HMGB1	PADI4	SPRY4	**Heart**	IL17RA	CRP	CD74	LILRB2	EBI3
ATXN3	HPRT1	PALMD	SRC	ACTA2	IL2	GBP5	CD80	LILRB4	IFITM3
AXL	HSP90AA1	PDCD1LG2	ST5	MYL9	IL2RB	IL10RA	CD84	LST1	IRF7
BASP1	HSPA12B	PDGFA	ST8SIA4	TRDN	IL4	IL17A	CD96	LTA	ISG20
BATF	HYAL1	PDGFRB	STAT1	**Kidney**	LCP2	IL17RB	CEACAM3	LTB	JUN
BATF3	HYAL2	PHEX	STAT3	AQP2	NFATC1	IL18	CHUK	LTF	MX1
BDNF	IER5	PIN1	STAT5A	KAAG1	NFATC2	IL18BP	CIITA	LY96	
BLK	IFIT1	PLAAT4	STAT5B	NPHS1	RAG2	IL18RAP	CPA3	MCAM	
BMP2	IFITM1	PLAT	SYK	NPHS2	REL	IL1RL1	CSF3	MICA	**INTERNAL REFERENCE GENES**
BMP4	IFITM2	PLAU	TANK	SLC12A3	RELB	IL22	CTSS	MICB	
BMP6	IFNAR1	PLAUR	TAP1	UMOD	SELE	NFKB2	CTSW	MIF	ABCF1
BMP7	IFNAR2	PLK2	TAP2	**Liver**	SH2D1A	NFKBIA	CXCL14	MME	G6PD
BMPER	IGF1R	PNOC	TBK1	FABP1	SH2D1B	NFKBIZ	CXCL16	MPIG6B	GUSB
BMPR1A	IGF2R	PPM1F	TEK	HNF1A	THEMIS	PTX3	DEFB1	MRC1	NRDE2
BMPR1B	IGFL1	PPP3CA	TFF3	IGFBP1	TNFRSF17	TNF	EOMES	MS4A1	OAZ1
BRWD1	IMPDH1	PRDM1	TGFB1	KRT19	TNFRSF18	TNFAIP3	FCER1G	MS4A2	POLR2A
BTG2	IMPDH2	PROX1	TGFB2	KRT8	TNFSF4	TRAF4	FCGR1A	MS4A4A	PPIA
CD207	INHBC	PSEN1	TGFBI	**Lung**	TNFSF8	**Innate Immune System**	FCGR2B	MS4A6A	SDHA
CD38	IRS1	PSMB10	TGFBR1	MYOM2	TRAT1	B2M	FCRL2	MS4A7	STK11IP
CD44	ISG15	PSMB8	TGFBR2	SFTPA2	TRDC	BCL3	FGFBP2	MYD88	TBC1D10B
CD47	ITGA4	PSMB9	TGIF1	SFTPB	TRDV3	CCR1	FJX1	NCAM1	TBP
CD81	ITGB2	PSME1	THBD	SFTPC	XBP1	CCR6	GZMA	NCR1	UBB
CD82	TGB6	PSME2	THBS1	SFTPD	ZAP70	CD14	HAVCR2	NFAM1	

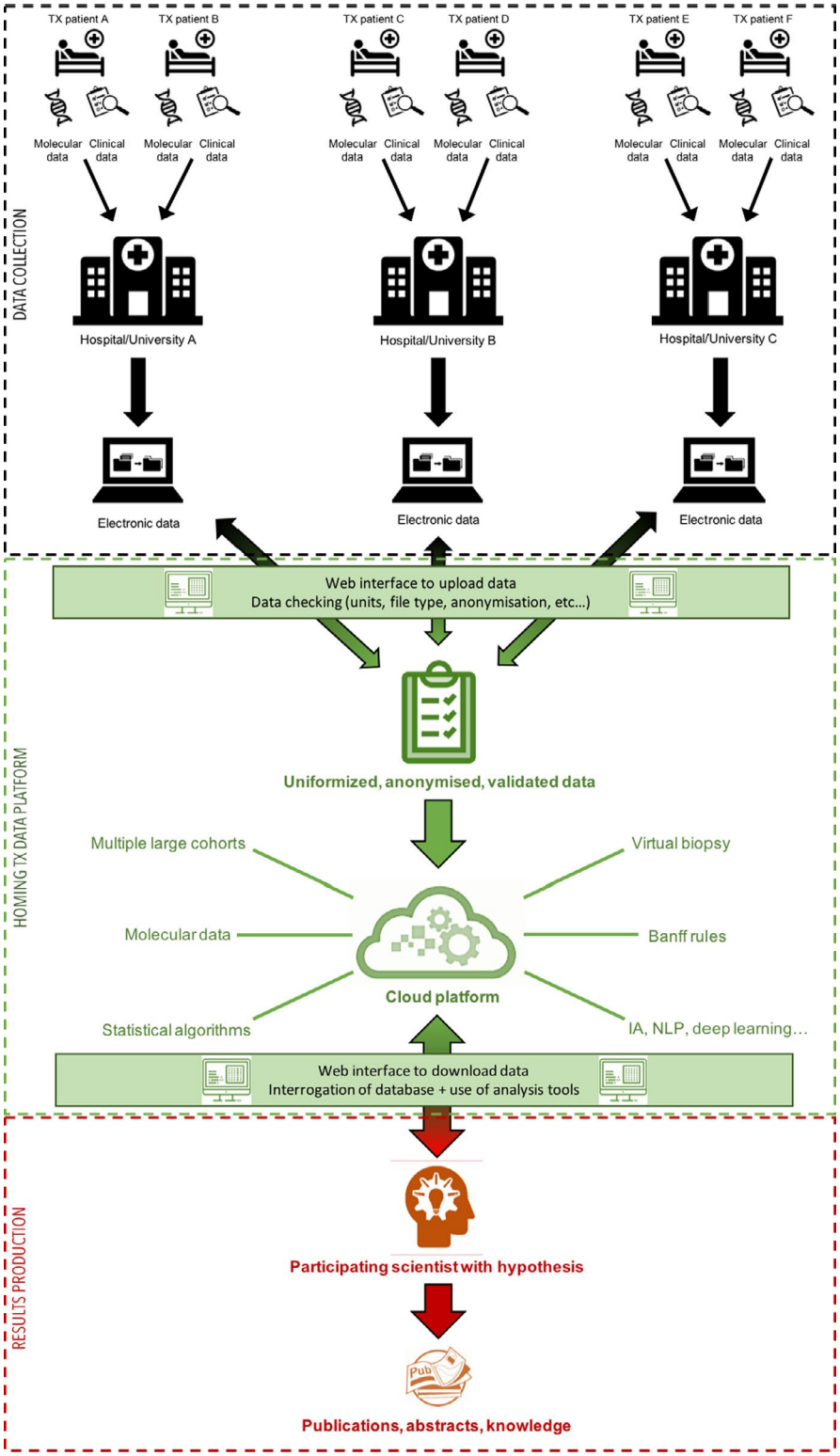

FIGURE 3 Data integration platform (DIP) design. Three elements are identified: (1) data production (histology, molecular, and clinical) by participating hospital; (2) DIP (web interface, cloud computing) to centralize, check, and validate all data; and (3) results production by any participating physician/scientist using built in analytical tools

developed test remains to be seen. If it does, it will probably be a simplified panel. In the future, the international, open source, multicenter Banff DIP can serve as a reference point for generating a molecular diagnostic "gold-standard" in transplantation, similar to the Banff histology lesions and diagnoses agreed upon in 1991.[70] As the Banff consensus rules for histology underwent refinement over the last 28 years as new knowledge emerged, any molecular "consensus" will also need to undergo constant refinement and, no doubt further, technological innovation. Only through integration with clinical decision-making and end points in clinical trials can the true clinical utility of molecular diagnostics be demonstrated.[67]

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DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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